United States Court of Appeals for the Federal Circuit

97-1495, 98-1017

THE JOHNS HOPKINS UNIVERSITY,

BAXTER HEALTHCARE CORPORATION and

BECTON DICKINSON AND COMPANY,

Plaintiffs-Appellees,

v.

CELLPRO, INC.,

Defendant-Appellant.

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Appealed from: United States District Court for the District of Delaware

Judge Roderick R. McKelvie

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THE JOHNS HOPKINS UNIVERSITY, BAXTER HEALTHCARE CORPORATION, and BECTON DICKINSON AND COMPANY,

Plaintiffs-Appellees,

v.

CELLPRO, INC.,

Defendant-Appellant.

DECIDED: August 11, 1998

Before LOURIE, Circuit Judge, SMITH, Senior Circuit Judge, and SCHALL, Circuit Judge.

LOURIE, Circuit Judge.

CellPro, Inc. appeals from the decision of the United States District Court for the District of Delaware in favor of Johns Hopkins University, Baxter Healthcare Corporation, and Becton Dickinson and Company (collectively, Hopkins) in their patent infringement suit against CellPro. The court (1) granted Hopkins' motion for judgment as a matter of law that CellPro infringed claims 1-5 of U.S. Patent B1 4,714,680, see Johns Hopkins Univ. v. CellPro, 931 F. Supp. 303, 319 (D. Del. 1996) [hereinafter Hopkins I]; (2) excluded certain evidence allegedly relevant to the obviousness of those claims, see Johns Hopkins Univ. v. CellPro, Civ. No. 94-105- RRM (D. Del. Oct. 1, 1996); id. (D. Del. Jan. 29, 1997); (3) granted Hopkins' motion for summary judgment that CellPro infringed claims 1 and 4 of U.S. Patent 4,965,204, see id. (D. Del. Nov. 27, 1996); (4) granted Hopkins' summary judgment motion concerning CellPro's enablement and written description defenses, see id. (D. Del. Feb. 24, 1997) (enablement); id. (D. Del. Oct. 31, 1996) (written description); (5) sustained the jury's verdict of willful infringement and treble damages, see John[s] Hopkins Univ. v. CellPro, 978 F. Supp. 184 (D. Del. 1997) [hereinafter Hopkins II]; and (6) ordered certain vials of CellPro's product to be repatriated to the United States and destroyed, see Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jul. 24, 1997). We affirm-in-part, vacate-in-part, and remand.

BACKGROUND

A. The Technology

The '680 and '204 patents (the "Civin patents") issued from continuations of the same parent application 1 and pertain generally to relatively pure suspensions of immature blood cells and monoclonal antibodies used to produce such suspensions. These immature cells, known as "stem" cells, develop into many different forms of mature blood cells, including lymphoid cells (T-cells and B-cells) and myeloid cells (red cells, platelets and granulocytes). See generally Hopkins I, 931 F. Supp. at 308 (discussing the physiology of blood).

Because stem cells are killed by radiation therapy, these cells must be replaced in leukemia patients who have undergone this treatment. While bone marrow transplants can provide a patient with new stem cells, this procedure carries risks. Notably, the presence of mature cells in transplanted bone marrow can give rise to Graft Versus Host Disease (GVHD), a potentially fatal condition. Accordingly, one of the stated objectives of the invention of the Civin patents "is to provide a method for preparing a cell population useful for stem cell transplantation that is enriched in immature marrow cells and substantially free of mature myeloid and lymphoid cells." '680 patent, col. 2, ll. 1-5; see also Hopkins I, 931 F. Supp. at 309.

In the early 1980s, scientists began making monoclonal antibodies that would recognize and bind to the antigens contained on the surface of blood cells. Once an antibody binds to an antigen on a cell surface, that cell is flagged and can be separated from other cells using known techniques such as the "FACS" method. Monoclonal antibodies, which are uniform in their binding properties, are produced by cloned cells known as hybridomas. Hybridomas grow and reproduce rapidly and can be frozen for later use to produce additional monoclonal antibodies.

Dr. Curt Civin, the inventor named in the '680 and '204 patents, discovered an antigen, which he named My-10, that appears on the surface of immature stem cells but not on the surface of mature cells. The patents' specifications disclose a monoclonal antibody, which Civin named anti-My-10, which recognizes the My-10 antigen and is useful in separating stem cells from mature cells. The patents further disclose how a hybridoma which manufactures the anti-My-10 antibody can be produced and note that a sample of the hybridoma has been deposited with the American Type Culture Collection (ATCC), ATCC Accession No. HB-8483, in Rockville, Maryland.

The '680 and '204 patents claim, respectively, a purified cell suspension of stem cells and monoclonal antibodies useful in producing such a suspension. The parties do not draw distinctions between the various claims in the patents, and instead premise their arguments as to each patent solely on independent claim 1 of each patent. These claims are set forth below with the disputed limitations from each claim emphasized:

'680 Claim 1: "A suspension of human cells comprising pluripotent lympho-hemapoietic stem cells substantially free of mature lymphoid and myeloid cells."

'204 Claim 1: "A monoclonal antibody which specifically binds to an antigen on nonmalignant, immature human marrow cells, wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483. . . ."

B. CellPro's Activities and Accused Products

1. CellPro's Technology

Four years after the filing date of the parent application of the Civin patents, Dr. Ronald Berenson, a scientist at the Fred Hutchinson Research Center, developed a method of physically separating stem cells from mature cells that was similar to that disclosed in the Civin patents. The monoclonal antibody developed by Berenson for this purpose was designated the 12.8 antibody.

Berenson and others at Hutchinson formed CellPro in 1989 and obtained licenses from Hutchinson for the use of Berenson's cell separation technology. In July 1990, CellPro produced, by cloning, a master cell bank constituting 100 vials of 12.8 hybridoma. Some of these vials were subsequently thawed and cloned to create a working cell bank to produce the 12.8 antibody. CellPro began to sell two machines, the Ceprate LC and the Ceprate SC, which its customers used in conjunction with the 12.8 antibody to perform Berenson's cell separation method.

2. CellPro's Knowledge of the Civin Patents and its Procurement of Legal Opinions

At the time CellPro was formed, representatives of CellPro knew of the '680 cell suspension patent, which issued on December 12, 1987. They had also monitored the Official Gazette of the Patent and Trademark Office to determine if Civin had been issued any antibody-related patent; the '204 antibody patent, which issued on October 23, 1990, was so discovered. See Hopkins II, 978 F. Supp. at 187-88. CellPro does not in fact dispute that it was aware of the existence of the Civin patents when it began its allegedly infringing activity.

Ostensibly concerned that CellPro's activities might fall within the scope of the '680 patent, Thomas Kiley, a

member of CellPro's Board of Directors and the company's legal advisor, engaged the law firm of Lyon & Lyon LLP and its partner Coe Bloomberg in early April 1989 to provide an opinion on the validity of the claims of the '680 patent. Bloomberg apparently reported to the CellPro board in May and September 1989 that he had reviewed the prosecution history of the patent and had concluded that the patent was invalid. Bloomberg's oral opinion was first reduced to writing on February 27, 1990. That later written opinion concluded that the claims of the '680 patent were invalid over several pieces of prior art and were unenforceable for inequitable conduct. CellPro used Bloomberg's opinion letter to assist it in raising an additional $7.5 million from investors. See id.

In the spring of 1991, CellPro's board asked Bloomberg for an opinion concerning the '204 patent. Bloomberg apparently prepared a draft opinion and submitted it to Kiley, who reviewed it and provided Bloomberg with comments. This opinion, like the '680 opinion, concluded that the claims were invalid and unenforceable. Bloomberg also opined that CellPro did not infringe claims 2, 3, 5, and 6, but was silent as to infringement of claims 1 and 4, the claims asserted in this action. The '204 opinion letter was also used by CellPro as a mechanism for inducing investment in the company. In the prospectus accompanying CellPro's public offering, the company reported that "[b]ased on the advice of Lyon & Lyon, special patent counsel to the company, CellPro believes that [the Civin] patents are invalid and unenforceable." Id. at 189 (internal quotations omitted).

By December of 1991, CellPro had set aside $3 million as a reserve for potential litigation involving the Civin patents. CellPro also made provision in its financial forecasts for the possibility that it would litigate and lose, and be forced to pay a "stiff royalty" of 15% as damages. Id.

C. The District Court Litigation

1. Infringement

Hopkins, assignee of the Civin patents, and its licensees, Baxter Healthcare and Becton Dickinson, sued CellPro on March 8, 1994, alleging infringement of certain claims of the '204 patent. CellPro, inter alia, counterclaimed for a declaratory judgment of invalidity and noninfringement of certain claims of the '680 patent, prompting Hopkins to sue CellPro for infringement of that patent as well.

The case was tried to a jury beginning on July 24, 1995. The district court reserved construing the claims until after the presentation of evidence. At that time, the court considered but did not provide the jury with instruction concerning the meaning of the disputed limitations, concluding that the language contained therein could be understood according to its ordinary meaning. See Johns Hopkins Univ. v. CellPro, 894 F. Supp. 819, 827-28 (D. Del. 1995). The jury returned a verdict entirely favorable to CellPro, concluding that all of the asserted claims of both patents were invalid for obviousness and lack of enablement, and that none of the asserted claims was infringed. See Hopkins I, 931 F. Supp. at 307.

Hopkins brought a renewed motion for judgment as a matter of law and in the alternative moved for a new trial, asserting, inter alia, that the court had erred in its construction of the disputed claim limitations. The court agreed that its failure to construe the disputed limitations appeared to be in error, see id. at 313, 317, and revisited these and other questions in considering the motion.

a. The '680 Patent

As to the "substantially free" limitation of the '680 claims, the district court, in considering the motion, was "reluctant to impose mathematical certainty on an ambiguous term when [the] patent applicant has strenuously avoided doing so." Id. at 318. However, despite this reluctance, the court adopted a construction that required "a cell suspension of at least 90% purity"; in other words, "the cell suspension must contain no more than 10% mature lymphoid and myeloid cells" in order to be within the scope of the claims. Id. The court noted that its construction was consistent with the patent's specification and with expert testimony offered at trial. The court observed that while the specification did not explicitly define the meaning of the words "substantially free," the specification did acknowledge that the techniques used to assess the purity of My-10-positive populations "have not detected any appreciable number (i.e., not significantly above background) of normal mature . . . cells." '680 patent, col. 3, ll. 64-67. The court, however, found persuasive Civin's deposition testimony that one of ordinary skill would interpret the words "substantially free" in accordance with the limitations of the disclosed FACS cell separation technique which was capable of producing cell suspensions of 85-90% purity. Finally, the court noted that its construction was consistent with the patent's disclosure of the production of a stem cell suspension of 90% purity in Table 9. See Hopkins I, 931 F. Supp. at 318.

Following its first real construction of the words "substantially free," the court granted Hopkins' motion for judgment as a matter of law on the issue of literal infringement. The court noted that Hopkins could prove infringement without testing the accused cell suspensions, see id. at 319 (citing Allen Archery, Inc. v. Browning Mfg. Co., 819 F.2d 1087, 1098, 2 USPQ2d 1490, 1498 (Fed. Cir. 1987)), and it summarized the documentary evidence that showed that the cell suspensions produced by CellPro's cell separation technique were of greater than 90% purity. This evidence included a CellPro letter and brochure that explained that CellPro's Ceprate LC device had "achieved purities of 91.5%, 91.6%, and 93.7% during experimental runs of the device." Id. Additionally, a clinical study protocol stated that clinicians had "achieved up to 95% purity during experiments with the Ceprate SC." Id. The court concluded that, in light of this evidence, no reasonable jury could conclude that CellPro did not infringe the asserted claims of the '680 patent. Id.

The court also granted Hopkins' motion for a new trial on the issue of the obviousness of the asserted claims of the '680 patent, see id. at 321; 35 U.S.C. § 103 (1994), because, inter alia, the three references upon which CellPro relied to establish obviousness (viz., Civin, Koeffler, and Amato) were not listed on CellPro's pre-trial order and therefore were not properly before the jury. See Hopkins I, 931 F. Supp. at 320. In its subsequent preparation for the new trial on this issue, CellPro attempted to include evidence showing that the claims as finally construed were either anticipated or obvious in light of a publication by Morstyn. The court, however, ruled from the bench that it would not entertain any arguments concerning the Morstyn reference because such arguments were "based on . . . prior art that [CellPro] knew about before the prior trial" but failed to then rely upon. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Oct. 1, 1996) (transcript at 24). The court subsequently granted summary judgment of nonobviousness to Hopkins, concluding that CellPro had failed to raise a genuine issue of material fact that warranted a trial on this issue. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jan. 29, 1997).

b. The '204 Patent

The district court agreed with Hopkins that the "wherein" clause of the '204 claims referred to an antigen that was now more simply understood by those of ordinary skill in the field as the "CD34 antigen," and adopted a claim construction that reflected this understanding. Hopkins I, 931 F. Supp. at 314. The court noted that its

construction was "unorthodox" because it "defined a large number of words in the claim with reference to a single alphanumeric reference, CD34," but that this shorthand was warranted in light of the "difficulty of describing the antigen to which the '204 patent refers." Id. at 313. In rejecting CellPro's argument that the court's claim construction should not refer to CD34, but instead My-10, the antigen disclosed in the patent's specification, the court noted that:

Those skilled in the art of making monoclonal antibodies, however, clearly understand that My-10 and CD34 are the same. The attorney prosecuting the application for the '204 patent argued that My-10 was becoming known in the art as CD34 as a result of the International Leukocyte Workshops. The examiner recognized this when she observed that claim 1 "limits the claimed monoclonal antibodies to species that react with a particular antigen (now identified as CD-34)."

Id. at 314. Accordingly, the court concluded that the "wherein" clause was an "attempt to describe a specific physical entity, which those skilled in the art now call the CD34 antigen," and furthermore that any antibody which binds to this antigen would infringe the asserted claims. Id.

In light of this construction, the court granted Hopkins' motion for a new trial on the issue of literal infringement. The court concluded that "[t]he evidence offered at trial, including [that] through CellPro's own experts, establishes that the 12.8 antibody binds to the CD34 antigen." Id. at 316. Rather than grant Hopkins' renewed motion for judgment as a matter of law, the court at first allowed CellPro to attempt to establish a foundation to support its theories of noninfringement, which mostly hinged upon proof that the 12.8 antibodies bind to mature basophils. See id. at 316, 317. However, the court soon thereafter granted Hopkins' motion for summary judgment on the issue of literal infringement, essentially concluding that the evidence that the 12.8 antibody binds to different species was irrelevant given that it binds to the CD34 antigen. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Nov. 27, 1996).

The court also granted Hopkins' motion for a new trial concerning lack of enablement of the claims of the '204 patent. See Hopkins I, 931 F. Supp. at 322; 35 U.S.C. § 112, 1 (1994). In support of its defense, CellPro had argued that the specification does not teach one skilled in the art to make antibodies which bind to the CD34 antigen other than the disclosed anti-My-10 antibody, and accordingly that the full breadth of the asserted claims was not enabled. The court disagreed and concluded that:

the weight of the evidence suggests that the '204 patent is enabled. Despite the fact that CellPro's experts claim that the '204 patent i[s] not enabling, none of them can identify anything that is missing from the specification. By contrast, the specification states that Civin's hybridoma is on deposit for others to utilize. In addition, the specification describes the entire fusion process, including the immunogen, which is also on deposit, the specific type of mice immunized, and the use of the methodology utilized by Kohler and Milstein.[ ]

Hopkins I, 931 F. Supp. at 324. Hopkins subsequently moved for summary judgment. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Feb. 24, 1997). To rebut Hopkins' motion, CellPro offered evidence purporting to show that various experts either could not produce another antibody using the teachings of the patent or otherwise could do so only through undue experimentation. See id.; Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) (noting that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive."). The court did not find that CellPro's evidence raised

any genuine issue of material fact, and granted Hopkins' summary judgment motion. The court concluded that those "experts" to whom CellPro referred in support of its argument either were not experts, did not follow the teachings of the patent, or otherwise did not engage in undue experimentation. As to those experts that only had success in producing a suitable antibody after several attempts, the court concluded that "[r]outine repetition of a patent's specification to achieve a desired experimental result does not constitute undue experimentation." Johns Hopkins Univ. v. CellPro, Civ. No. 94-105- RRM, at 5 (D. Del. Feb. 24, 1997) (citing PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623-24 (Fed. Cir. 1996)).

CellPro further argued in the district court that the asserted claims of the '204 patent were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112, 1 (1994). The court, from the bench, granted CellPro permission to assert this defense, but then granted summary judgment to Hopkins' on the merits. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Oct. 31, 1996) (transcript at 12-13).

2. Damages and Willful Infringement

With CellPro's liability for infringement decided by the grant of Hopkins' various motions, the issues of damages and willful infringement were tried to a jury beginning March 4, 1997. See Hopkins II, 978 F. Supp. at 186. The jury assessed over $2.3 million dollars in damages and found CellPro's infringement to be willful. See id. at 191-92. Hopkins then moved for enhanced damages pursuant to 35 U.S.C. § 284. The court, noting that enhanced damages under section 284 are punitive in nature, see, e.g., Beatrice Foods Co. v. New England Printing & Lithographing Co., 923 F.2d 1576, 1580, 17 USPQ2d 1553, 1556 (Fed. Cir. 1991), applied the factors enumerated in Read Corp. v. Portec, Inc., 970 F.2d 816, 827, 23 USPQ2d 1426, 1435-36 (Fed. Cir. 1992), to determine the extent to which enhancement was appropriate. Central to the court's decision to treble damages, the maximum enhancement permissible under the statute, was its conclusion that Bloomberg's opinion letters were:

so obviously deficient, one might expect a juror to conclude that the only value they had to CellPro in the world outside the courtroom would have been to file them in a drawer until they could be used in a cynical effort to try and confuse or mislead what CellPro, its Board, and counsel must have expected would be an unsophisticated jury.

Hopkins II, 978 F. Supp. at 193. The district court was not convinced that the opinion letters provided CellPro with a good faith belief that the patents were invalid. See note 16, supra (second factor). Specifically, the court found the opinions to be untimely, not competent, and not relied upon by CellPro. See Hopkins II, 978 F. Supp. at 193.

3. The Repatriation Order

As part of the district court's permanent injunction order, Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jul. 24, 1997), the court ordered CellPro to repatriate to the United States "all clones or subclones of the 12.8 hybridoma cell line previously exported by it, as well as any further clones or subclones produced therefrom," and any antibodies produced therefrom. Id. at 3-4. This order encompassed six vials of 12.8 hybridoma from CellPro's United States cell bank which CellPro sent to its Canadian business partner, Biomira, Inc., and cloned vials and antibodies produced therefrom in Canada. These six vials, like the other vials in the cell bank, were created prior to the issuance of the '204 patent, the only patent that is relevant to the 12.8 hybridoma, but were sent to Canada during the term of that patent. The six vials

were never thawed or used in any manner prior to their export. One of the six vials was cloned in Canada to produce a working Canadian cell bank of 32 vials of 12.8 hybridoma. Under CellPro's contract with Biomira, Biomira thawed and used the hybridoma from the Canadian cell bank to make 12.8 antibodies for the performance of the Berenson cell separation technique in Canada. Title to the hybridoma, however, remained with CellPro.

In its memorandum opinion supporting its repatriation order, the court did not find compelling CellPro's argument that none of its activities concerning the six vials exported to Canada were infringing uses under 35 U.S.C. § 271 and that they were thus free of the court's equitable power to order repatriation:

CellPro argues that because it shipped cells that were part of the original batch of noninfringing cells—rather than those that were cloned [after the issuance of the '204 patent in the United States]—it did not run afoul of § 271(a). The court finds this distinction to be immaterial. CellPro created the 12.8 hybridoma with the intention of developing a bank of identical cells to produce a monoclonal antibody—the 12.8 antibody. Thus, by using some cells in the [United States cell] bank for the purpose of cloning or testing, it is committing an infringing "use" with respect to the bank as a whole.

Accordingly, because CellPro created and maintained its hybridoma in Canada as a result of infringing activities in the United States, the court finds that it will be acting within its equitable powers under 35 U.S.C. § 283 by ordering CellPro to repatriate the hybridomas stored at Biomira. Doing so would tend to reestablish the status quo as it existed before CellPro willfully infringed the asserted claims of the '204 patent.

Id. at 27 (memorandum opinion).

CellPro appealed numerous points of error to this court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1) (1994).

DISCUSSION

A. Standard of Review

Judgment as a matter of law (JMOL) is appropriate when "a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." Fed. R. Civ. P. 50(a)(1). We review a district court's decision on a motion for JMOL de novo, reapplying the JMOL standard. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 975, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995) (in banc), aff'd, 517 U.S. 370, 38 USPQ2d 1461 (1996). Summary judgment is appropriate when there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). We similarly review a district court's grant of summary judgment de novo, reapplying the summary judgment standard. See Conroy v. Reebok Int'l, Ltd., 14 F.3d 1570, 1575, 29 USPQ2d 1373, 1377 (Fed. Cir. 1994).

"[T]he determination whether a claim has been infringed requires a two-step analysis: First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process." Carroll Touch, Inc. v. Electro Mechanical Sys., Inc., 15 F.3d 1573, 1576, 27 USPQ2d 1836, 1839 (Fed. Cir. 1993). The first step, claim construction, is a question of law, which we review de novo. See Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1174 (Fed. Cir. 1998) (in banc). The second step is factual. See North Am. Vaccine, Inc. v.

American Cyanamid Co., 7 F.3d 1571, 1574, 28 USPQ2d 1333, 1335 (Fed. Cir. 1993). When construing a claim, a court principally consults the evidence intrinsic to the patent, viz., the claims themselves, the written description portion of the specification, and the prosecution history. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582-83, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Whether making and using an invention would have required undue experimentation, and thus whether a disclosure is enabling under 35 U.S.C. § 112, 1 (1994), is a legal conclusion based upon underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988).

Because courts have broad discretion in determining the scope of injunctive relief under 35 U.S.C. § 283 (1994), we review the scope of a district court's permanent injunction for an abuse of discretion. See Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 945, 22 USPQ2d 1119, 1127 (Fed. Cir. 1992). Likewise, the propriety of an evidentiary ruling by the district court is reviewed for an abuse of discretion. See Kearns v. Chrysler Corp., 32 F.3d 1541, 1547, 31 USPQ2d 1746, 1750 (Fed. Cir. 1994); In re Merritt Logan, 901 F.2d 349, 359 (3rd Cir. 1990).

Whether infringement was willful is a question of fact, and we will not reverse a jury determination on this issue unless it was unsupported by substantial evidence. See Hoechst Celanese Corp. v. BP Chems. Ltd., 78 F.3d 1575, 1583, 38 USPQ2d 1126, 1132 (Fed. Cir. 1996). A district court's decision to enhance damages for willful infringement and the extent of the enhancement is reviewed for an abuse of discretion. See SRI Int'l, Inc. v. Advanced Tech. Labs., Inc., 127 F.3d 1462, 1468, 44 USPQ2d 1422, 1427 (Fed. Cir. 1997).

B. Validity and Infringement of the '680 Patent

1. Claim Construction and Infringement

CellPro asserts that the district court's construction of the "substantially free" limitation to require no more than 10% mature cells was in error. Instead CellPro believes that this limitation should be construed to mean an immeasurable amount of mature cells. Accordingly, CellPro contends that JMOL of infringement was erroneously granted, because cell suspensions produced by its technique and equipment contained measurable amounts of mature cells numbering in the "millions."

To support its claim construction, CellPro points to the prosecution history of the '680 patent, which progressed in relevant part as follows: The examiner rejected the claims as anticipated by two prior art publications by Bodger et al. The applicant responded by noting that Bodger's antibodies could not be used to produce a cell suspension that was "substantially free" of mature cells as required by the claim language. The examiner was not persuaded and noted that "[t]he metes and bounds of 'substantially free' have not been established" by the applicant, to which the applicant responded:

"Substantially free" is defined by its plain meaning and further by the stated characteristics of the anti-My-10 antibody . . . . At page 5, lines 27-31, of the specification [see '680 patent, col. 6, ll. 62-67] it is explicitly stated, "Various assay techniques have been employed to test for the presence of the My-10 antigen, and those techniques have not detected any appreciable number (i.e., not significantly above background) of normal, mature human myeloid and lymphoid cells in My-10-positive populations." For example, when My-10+ cells are incubated with a series of monoclonal antibodies which react with T-lymphocytes [i.e., a type of mature cell], no cells are found to be reactive. Thus, by the means presently available to the art, no T-lymphocytes are found in My-10+ cell populations.

(emphasis in original). The applicant also noted that "Bodger's cell population has some T-cells present, but [that] the present invention has none," and therefore that Bodger's cell suspension would be ineffective in preventing GVHD.

Hopkins responds that the district court's claim construction was correct and was consistent with the intrinsic evidence. Hopkins notes that the specification, reflecting the imperfect state of the art and specifically the imperfect nature of cell separation techniques such as the FACS method, teaches that the disclosure concerning preparation of antibodies would enable the creation of only "relatively pure" stem cell suspensions. See '680 patent, col. 4, ll. 55. Hopkins asserts that the highest disclosed purity for a stem cell suspension created by the disclosed technique, viz. 90%, see '680 patent, col. 18, tbl. 9, should define the outer bounds of the words "substantially free." Hopkins argues that CellPro's proposed claim construction and citation from the prosecution history are inconsistent with Table 9, which describes small but measurable amounts of mature cells.

We agree with Hopkins that the district court's construction of the words "substantially free" was not in error. Table 9, the only disclosed embodiment of the claimed cell suspension, is highly indicative of the scope of the claims. A patent claim should be construed to encompass at least one disclosed embodiment in the written description portion of the patent specification. This maxim flows from the statutory requirement that "[t]he specification shall contain a written description of the invention," 35 U.S.C. § 112, 1 (1994), which requires a patent applicant to disclose in the specification sufficient subject matter to support the breadth of his claim. See Specialty Composites v. Cabot Corp., 845 F.2d 981, 987, 6 USPQ2d 1601, 1604 (Fed. Cir. 1988) (noting that what is patented "is defined by the words in the claims if those claims are supported by the specification in the manner required by 35 U.S.C. § 112."); Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1219, 36 USPQ2d 1225, 1230-31 (Fed. Cir. 1995). A claim construction that does not encompass a disclosed embodiment is thus "rarely, if ever, correct and would require highly persuasive evidentiary support." Vitronics, 90 F.3d at 1583, 39 USPQ2d at 1578. Accordingly, CellPro's claim construction, that the cell suspension of the claims can contain only an immeasurable amount of mature cells, is undermined by Table 9 of the specification, which describes the only embodiment of the invention disclosed in the specification and discloses a cell suspension that contains 3% mature neutrophils, 6% mature monocytes, and 1% mature lymphocytes, all of which constitute measurable quantities of mature lymphoid cells. See '680 patent, col. 18, tbl. 9 n.*.

CellPro also notes that in response to the examiner's request to clarify the "metes and bounds" of the words "substantially free," the applicant, quoting the specification, noted that "[v]arious assay techniques have been employed to test for the presence of the My-10 antigen, and those techniques have not detected any appreciable number (i.e., not significantly above background) of normal, mature human myeloid and lymphoid cells in My-10-positive populations." However, this passage does not describe the purity of a cell suspension produced by the disclosed technique, but rather describes the various species of cells that are present in "My-10-positive populations," i.e., in populations which express the My- 10 antigen. Thus, the quoted passage merely clarifies that a population of cells expressing the My-10 antigen contains no "appreciable number" of mature cells; it does not support the inference that such a population, when included with other mature cells and sorted according to the technique disclosed in the '680 patent, can be sorted to recover only My-10-positive cells. Not only is this inference directly contrary to the reality of the cell suspension disclosed in Table 9, but it is also contrary to the expert testimony at trial which established that sorting techniques such as FACS suffer from "practical limitations" and are capable of producing cell suspensions of only 85-90% purity, the upper value of which is consistent with the district court's construction. See Hopkins I, 931 F.

Supp. at 318. Moreover, the record is silent concerning the expected background levels for mature cells in a sorted cell suspension. Thus, reference to "background level" sheds little light on the construction of the words "substantially free."

CellPro next calls attention to the prosecution history in which the applicant notes that "when My-10+ cells are incubated with a series of monoclonal antibodies which react with T-lymphocytes, no cells are found to be reactive." Like the portion of the prosecution history cited above, this statement does not address the purity of a suspension produced by separation.

Finally, the applicant's statement that "Bodger's cell population has some T-cells present, but the present invention has none" does not support CellPro's proffered construction. That the inventive cell suspension might contain no (or an immeasurable amount of) T-cells does not mean that the cell suspension does not contain measurable amounts of other mature myeloid and lymphoid cells. Table 9 illustrates this point. Mature lymphocytes, of which T-cells are a subset, constituted a mere 1% of the stem cell suspension. However, other mature cells, including neutrophils (3%) and monocytes (6%), were also present in the suspension. See note 10, supra. In the end, it is unremarkable that the claims issued over Bodger, a reference which disclosed the use of an antibody that, unlike My-10, was specifically reactive with T-cells and consequently produced a cell suspension that was not substantially free of mature lymphoid cells.

Thus, none of the statements in the prosecution history that CellPro cites constitutes "highly persuasive" evidence to suggest that we should deviate from a claim construction that is required in order to encompass the only disclosed embodiment of a cell suspension in the '680 patent. We therefore affirm the district court's construction of the language "substantially free of mature lymphoid and myeloid cells" as requiring no more than 10% mature lymphoid and myeloid cells and its grant of JMOL in favor of Hopkins on the issue of literal infringement.

2. Obviousness/Anticipation

CellPro argues that it was error for the court, after granting Hopkins' motion for a new trial on the issue of obviousness, to exclude the Morstyn reference as evidence of obviousness. CellPro asserts that it should not be held to have "waived" its right to rely on the Morstyn reference simply because it knowingly chose not to rely on Morstyn during the first trial. CellPro argues that Morstyn, which CellPro characterizes as enabling one of ordinary skill in the art to produce a stem cell suspension of 90% purity, did not become pertinent until after the first trial when the court adopted its "broadened" construction of the words "substantially free." CellPro asserts that Morstyn, alone or in combination with Beverley, raises a genuine issue of material fact concerning the validity of the claims of the '680 patent and should have precluded summary judgment in favor of Hopkins on the issue of obviousness. Hopkins responds that CellPro waived its right to subsequently rely on Morstyn by virtue of its failure to include Morstyn in the final pretrial order pursuant to Fed. R. Civ. P. 16(e). Thus, according to Hopkins, the district court did not err in failing to consider invalidity arguments premised upon Morstyn.

We agree with CellPro that the district court erred in failing to consider CellPro's Morstyn-based invalidity challenge. The district court, when it construed the claims after trial, changed the rules of the game. Specifically, when the court rendered its claim construction of the words "substantially free" to encompass cell suspensions of at least 90% purity, new prior art became potentially relevant to the validity of those claims. CellPro was entitled to present this new art following the court's grant of Hopkins' new trial motion so that

Morstyn could be evaluated on its merits. That CellPro knew of Morstyn before the first trial but chose not to rely upon it then cannot constitute a waiver to apply that art against a claim whose construction was not yet finally determined by the court.

Our conclusion is not altered by Hopkins' "pretrial order" argument, because this argument has no merit. Nothing in Rule 16(e) indicates that a pretrial order from a first trial controls the range of evidence to be considered in a second trial. Indeed, such a cramped interpretation of Rule 16(e) would greatly hobble the parties from meaningfully relitigating an issue which the court has decided required retrial under Rule 59.

Accordingly, the court erred in determining that CellPro had waived its right to rely on the Morstyn reference to establish that the claims of the '680 patent were either anticipated or would have been obvious to one of ordinary skill. We therefore vacate and remand so that the Morstyn reference can be considered on its merits.

C. Validity and Infringement of the '204 Patent

1. Claim Construction and Infringement

CellPro asserts that the district court erred in construing the "wherein" clause of the '204 patent as referring to "the CD34 antigen." CellPro contends that reference to "the CD34 antigen" was unnecessary and incorrect: it was unnecessary because the "wherein" clause clearly refers to a single antigen, the My-10 antigen, that is disclosed in the specification; it was incorrect, CellPro continues, because "CD34" refers to a genus of antigens and thus erroneously sweeps into the claims all CD34 antibodies, regardless whether they bind to the My-10 antigen. CellPro states that what the scientific community refers to as "the CD34 antigen" is in fact "a collection of different molecules, all based on the same protein backbone, [with] a number a molecular forms." CellPro's Opening Brief at 32 (quoting its expert's declaration). Apparently CellPro considers these different molecules to be different antigens, because it explains that its 12.8 antibody binds to "a CD34 antigen" that is different from My-10. CellPro's Reply Brief at 13 (emphasis added).

Significantly, Hopkins agrees with CellPro that the claims cover a single antigen, not a genus of antigens, but contends that "the CD34 antigen" is an apt description of that claimed antigen. In support of its position, Hopkins points, inter alia, to the prosecution history. Specifically, Hopkins highlights the applicant's reference during prosecution to the conclusion of the Third International Workshop on Leukocyte Differentiation ("Workshop") and the applicant's statement to the examiner that "[t]he antigen recognized by the monoclonal antibodies of this invention has been designated My-10 . . . by the inventor, and subsequently CD-34 (antibody cluster designation) by the [Workshop]." The Workshop's report, also submitted by the applicant to the examiner, describes the antigen to which anti- My-10 is bound as "the CD34 antigen." In support of the district court's grant of summary judgment of infringement, Hopkins points to several other pieces of documentary evidence in which CellPro admits either that its 12.8 antibody binds to "the CD34 antigen" or otherwise binds to the same antigen as anti- My-10. Thus, Hopkins contends that CellPro infringes the claims regardless whether the antigen of the claims is referred to as "the CD34 antigen," "My-10," or (to paraphrase the "wherein" clause) "the antigen bound by the antibody produced by the hybridoma on deposit."

We agree with Hopkins that the district court's claim construction was not in error. The district court may have been correct that it was "unorthodox" to condense the meaning of the "wherein" clause into the simpler language of "the CD34 antigen." However, this treatment was not erroneous, as Hopkins' citations from the prosecution history show; the applicant directly equated My-10 and thereby the entirety of the "wherein"

clause with what the scientific community had come to understand as "the CD34 antigen." Furthermore, the record makes clear that the term "the CD34 antigen" is synonymous with the antigen discovered by Civin.

CellPro cites no intrinsic evidence and no credible extrinsic evidence in support of its theory that "the CD34 antigen" encompasses a genus of antigens. Instead, what the evidence does show is that the CD34 antigen contains a number of epitopes on its surface to which the various CD34 antibodies can bind. For example, the Workshop report explains that the various CD34 antibodies known as of that date all bind to the CD34 antigen, but to different epitopes, Joint App. at EA7275-82, and one study concluded that "at least three distinct CD34 epitopes" were expressed on the surface of the CD34 antigen, id. at EA7283. The same conclusion is confirmed by CellPro's own internal documents. For example, Dr. Berenson concluded that "[Antibody 12.8] recognizes the same antigen as does [anti-]My-10 . . . . Unlike [anti-My-10], antibody 12.8 recognizes a distinct epitope that is also present on a similar population of marrow cells in nonhuman primates." Id. at A1390. Other evidence supports the conclusion that 12.8 and anti-My-10 bind to the same antigen, see id. at A5846 (testimony of CellPro's expert, Dr. D.R. Sutherland) ("So collectively we think that this data suggests that the [anti-]My-10 and 12.8 binding sites are distinct and nonoverlapping binding sites on the CD34 molecule."); id. at EA5462 (Bloomberg '204 opinion letter) ("It is our understanding, based upon discussions with CellPro scientists, that the monoclonal antibody used by CellPro does not bind to the same epitope in the My-10 antigen as does the Civin anti-My-10 monoclonal antibody."), and that this antigen is the CD34 antigen, see id. at EA3781 (CellPro's FDA filing) ("The primary reagent is a monoclonal antibody (Mab) 12.8 which specifically binds to a unique antigen (CD34) on the target cells (stem cells).").

CellPro cites no evidence to refute the clear conclusion to be drawn from these documents that its 12.8 antibody binds to the CD34 antigen, albeit to a different epitope than does the anti-My-10 antibody disclosed in the patent, and therefore literally infringes the claims of the '204 patent. Accordingly, the district court's construction of the "wherein" clause and its subsequent grant of summary judgment of infringement are affirmed.

2. Enablement

CellPro argues that the claims of the '204 patent, which both parties agree are drawn to the genus of antibodies which bind to the claimed antigen, are not enabled as required by 35 U.S.C. § 112, 1, and that the district court erred in granting summary judgment to the contrary. CellPro contends that the patent discloses only the method of producing the anti-My-10 antibody and is therefore insufficient to enable one of ordinary skill in the art to make and use the broader genus of claimed antibodies. See, e.g., Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) ("To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.") (citation and quotation omitted). In support, CellPro points to evidence that it believes conclusively shows that one of ordinary skill following the techniques disclosed in the patent could produce other antibodies only after undue experimentation, and contends that this evidence should have precluded summary judgment.

Hopkins responds that the patent's disclosed method of producing antibodies, the Kohler/Milstein method, has been used to produce over forty additional CD34 antibodies, and that most of these antibodies, including CellPro's 12.8 antibody, see Hopkins I, 931 F. Supp. at 323, were produced using the disclosed preferred immunogen, the KG-1a cell line. See note 14, supra (outlining the Kohler/Milstein method); '204 patent, col. 3, ll. 41-50 & col. 5, ll. 30- 47. Hopkins further asserts that CellPro's evidence of undue experimentation is

insufficient to preclude entry of summary judgment.

When ruling on Hopkins' motion for summary judgment of enablement, the district court was obliged to have viewed the evidence in the light most favorable to the nonmoving party, in this case CellPro, and to have resolved any evidentiary doubts in CellPro's favor. See C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc., 991 F.2d 670, 672, 15 USPQ2d 1540, 1542 (Fed. Cir. 1990). Moreover, the court must have "view[ed] the evidence presented through the prism of the substantive evidentiary burden" that would inhere at trial. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 254 (1986). This burden rested upon CellPro, who had to prove by clear and convincing evidence facts establishing a lack of enablement. See Morton Int'l Co. v. Cardinal Chem. Co., 5 F.3d 1464, 1469, 28 USPQ2d 1190, 1194 (Fed. Cir. 1993); 35 U.S.C. § 282 (1994). However, CellPro's evidence must have done more than simply raise some doubt regarding enablement: "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." Anderson, 477 U.S. at 249-50 (citations omitted). Instead, CellPro's evidence must have shown that a material factual dispute existed, i.e., a dispute upon which a reasonable jury could have resolved enablement in CellPro's favor after a review of the entire record. See Sweats Fashions, Inc. v. Pannill Knitting Co., 833 F.2d 1560, 1562, 4 USPQ2d 1793, 1795 (Fed. Cir. 1987). Our review of the entire record leads to the conclusion that CellPro failed to raise a genuine issue of material fact concerning enablement, and therefore that the district court did not err in granting summary judgment. We consider each piece of CellPro's evidence in turn.

CellPro first contends that Civin's laboratory never again succeeded in producing another CD34 antibody using the technique disclosed in his patent specification despite a "major effort" on his part to do so. However, as the district court noted upon granting Hopkins' motion for a new trial on enablement, CellPro failed to offer evidence that many of those working on projects in Civin's lab, including undergraduate students or others who had never before made a monoclonal antibody, were of ordinary skill in the art. Hopkins I, 931 F. Supp. at 323. Despite being warned of this evidentiary shortcoming, CellPro thereafter apparently produced no evidence concerning the level of skill of those individuals working under Civin's supervision. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM, at 5. Because it is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation, see Genentech, supra, CellPro's evidence concerning Civin's subsequent work is insufficient as a matter of law.

CellPro next contends that the testimony of its expert, Dr. D.R. Sutherland, raises a genuine issue of material fact concerning enablement. Sutherland testified that he was unsuccessful in making a CD34 antibody. However, and as the district court noted upon granting Hopkins' motion for a new trial, Sutherland "did not use the screening technique disclosed in the specification" for identifying suitable hybridomas. Hopkins I, 931 F. Supp. at 323. A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. Because Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law.

CellPro also cites the expert declaration of Dr. John Wijdenes in an attempt to prove that the amount of experimentation needed to successfully practice the invention disclosed in the '204 patent was undue. Although Wijdenes concluded that it was generally "more difficult" for him to produce a CD34 antibody than other monoclonal antibodies, he did not attribute this difficulty to any shortcomings in the disclosure of the '204 patent. Instead, Wijdenes's declaration suggests that the Kohler/Milstein technique was not foolproof,

and that success with this technique commonly required repetition. This lack of certainty was thus not attributable to a failure of disclosure in the '204 patent. Such routine experimentation does not constitute undue experimentation:

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted); see also In re Wands, 858 F.2d 731, 736- 40, 8 USPQ2d 1400, 1403-07 (Fed. Cir. 1988) (applying this principle in the context of monoclonal antibody production). Furthermore, Wijdenes explained that the relative difficulty that was encountered in producing CD34 antibodies may have been due to the weak immunogenicity of the KG-1a cell line, see Joint App. at A23360, not because of an insufficiently enabling disclosure. In any event, Wijdenes was able to produce six CD34 antibodies using the KG-1a immunogen, see id. at A23361, and he noted that seven other CD34 antibodies were successfully manufactured using the KG-1 immunogen, see id. at A23343, which, if anything, suggests that the disclosure of those immunogens in the patent was sufficient to enable those of ordinary skill to produce a host of CD34 antibodies.

CellPro finally contends that no one ever succeeded in making CD34 antibodies using either purified My-10+ cells or immuno-precipitated My-10 antigens as the immunogens in the Kohler/Milstein method. See Hopkins I, 931 F. Supp. at 323. Hopkins argues that this fact, even if true, is legally irrelevant because the use of these immunogens was disclosed in the patent specification as alternatives to the preferred use of the KG-1/KG-1a cell line. See '240 patent, col. 5, l. 65 to col. 6, l. 27. Hopkins is correct; CellPro can carry its burden only by showing that all of the disclosed alternative modes are insufficient to enable the claims, because "[t]he enablement requirement is met if the description enables any mode of making and using the invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). CellPro's silence concerning enablement by use of the KG-1/KG-1a cell lines makes its argument on this point specious.

In conclusion, our consideration of the record makes clear that CellPro has not raised a genuine factual dispute concerning the enablement of the claims of the '204 patent. We therefore affirm the district court's grant of Hopkins' summary judgment motion on this issue.

3. Written Description

CellPro also asserts that the claims of the '204 patent are invalid under § 112, 1, because they lack an adequate written description. Specifically, CellPro relies on Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997), cert. denied, 118 S. Ct. 1548 (1998), which held that a genus of vertebrate or mammalian insulin cDNA was not adequately described by the patent's disclosure of a single species of rat insulin cDNA. CellPro argues by analogy that the claims of the '204 patent are invalid because they disclose only a single antigen and antibody. Hopkins responds that this court should not entertain CellPro's written description challenge because CellPro did not present it to the district court and therefore cannot raise it for the first time on appeal.

We agree with Hopkins. Our review of the record shows that CellPro's written description argument in the

district court was premised on the argument that the claims of the '204 patent would encompass monoclonal antibodies that bind to antigens on mature cells, but that the written description did not describe this aspect of the invention and in fact expressly disclaimed an invention of such broad scope. See Joint App. at A19087.5, A19296-98. This is not the Lilly- based written description argument that CellPro currently asserts on appeal.

CellPro also cites a document that it filed in the district court (only one page of which is included in the appendix filed in this court) in support of its contention that it raised a Lilly-based challenge in the district court. See Joint App. at A18371. However, in that page, CellPro merely mentioned the "genus-species" problem addressed by Lilly in a footnote; it did not make a serious Lilly-based argument as an alternative to its argument that the claims erroneously encompassed antibodies that bound to mature cells. Moreover, the main purpose of the document was to argue that the sufficiency of a written description under § 112, 1, is a question of fact. As a general rule, an appellate court will not hear on appeal issues that were not clearly raised in the proceedings below. See Singleton v. Wulff, 428 U.S. 106, 120 (1976); Braun, Inc. v. Dynamics Corp. of Am., 975 F.2d 815, 821, 24 USPQ2d 1121, 1126 (Fed. Cir. 1992). This rule ensures that "parties may have the opportunity to offer all the evidence they believe relevant to the issues . . . [and] in order that litigants may not be surprised on appeal by final decision there of issues upon which they have had no opportunity to introduce evidence." Hormel v. Helvering, 312 U.S. 552, 556 (1941). CellPro's casual reference in a footnote was insufficient to place its Lilly-based written description argument in issue before the district court. We therefore decline to address the merits of this argument on appeal.

D. Willful Infringement/Enhanced Damages

CellPro argues several points of error relevant to the district court's decision to treble damages. We consider each of these arguments in turn, but are not persuaded that any reversible error has occurred.

CellPro contends that the jury's finding of willfulness cannot stand because it is premised upon two errors committed by the district court. CellPro first asserts that the court erred in excluding from the jury evidence that CellPro had been wholly successful in the first trial, evidence that CellPro argues bears on the reasonableness of its actions. CellPro states that the test for willful infringement is "whether, under all the circumstances, a reasonable person would prudently conduct himself with any confidence that a court might hold the patent invalid or not infringed," State Indus., Inc. v. Mor-Flo Indus., Inc., 883 F.2d 1573, 1581, 12 USPQ2d 1026, 1032 (Fed. Cir. 1989), and that its vindication in the first trial is part of the "totality" of the evidence that should have been considered in a proper willfulness determination. See, e.g., Studiengesellschaft Kohle v. Dart Indus., Inc., 862 F.2d 1564, 1573, 9 USPQ2d 1273, 1282 (Fed. Cir. 1988) (noting that willful infringement can be found "only after due consideration of the totality of the circumstances"). Hopkins responds that the prior jury verdict is irrelevant because, inter alia, it was rendered in 1995, at least four years after CellPro learned of the Civin patents and thereafter continued to infringe. Alternatively, Hopkins contends that even if the prior verdict was relevant, the court had discretion under Fed. R. Evid. 403 to exclude it because the potential for unfair prejudice and confusion that might have resulted from the jury's consideration of this erroneous verdict outweighed the probative value of the fact of the verdict.

We agree with Hopkins that the district court did not abuse its discretion in excluding the existence of the prior liability verdict from the subsequent trial on willfulness and damages. First, as Hopkins notes and CellPro does not dispute, CellPro had notice of the '680 patent by 1989 and the '204 patent by 1991.

Because such notice placed upon CellPro on those dates the duty to exercise due care to determine whether or not it was infringing, see, e.g., Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1579, 230 USPQ 81, 90 (Fed. Cir. 1986), they were the proper times for assessing CellPro's willfulness. See, e.g., Datascope Corp. v. SMEC, Inc., 879 F.2d 820, 828-29, 11 USPQ2d 1321, 1327 (Fed. Cir. 1989). The 1995 jury verdict had no bearing upon the willfulness of CellPro's infringement on the dates it received notice of Hopkins' patent rights. Moreover, we agree with Hopkins that consideration of the 1995 jury verdict, which was ultimately determined to be premised upon an erroneous claim construction, had significant potential to confuse the jury. Cf. Texas Instruments v. Cypress Semiconductor Corp., 90 F.3d 1558, 1569 n.11, 39 USPQ2d 1492, 1502 n.11 (Fed. Cir. 1996) (upholding exclusion of the ITC's non-binding claim construction from a subsequent district court jury). In sum, we conclude that CellPro has not met its burden of showing that the district court abused its discretion in excluding the fact of the 1995 liability verdict from the willfulness jury.

CellPro also argues that the jury's willfulness finding cannot stand because the jury instructions erroneously mandated the jury to find that its infringement had been willful. CellPro points to the statements in the instructions to the effect that "no reasonable jury" could fail to find either that CellPro infringed the '680 and '204 patents or that these patents were valid. CellPro contends that these statements, coupled with the court's subsequent definition of willful infringement, i.e., "that the infringer had no reasonable basis for believing it had a right to engage in the infringing acts," forced a finding of willful infringement, because, according to CellPro, if no reasonable juror could have reasonably found the patents invalid or not infringed, it would likewise necessarily have been unreasonable for CellPro to have had such a belief.

We do not accept CellPro's argument. That no reasonable jury could fail to find that CellPro infringed valid patents says nothing about CellPro's willfulness, a determination which is reflective of an infringer's culpability. See Rite-Hite Corp. v. Kelley Co., 819 F.2d 1120, 1126, 2 USPQ2d 1915, 1919 (Fed. Cir. 1987) ("The term 'willfulness' thus reflects a threshold of culpability in the act of infringement . . . ."). The district court's statements concerning infringement and validity were properly designed to ensure that the willfulness jury didn't collaterally consider CellPro's liability for infringement in its deliberations. Prior to its instructions on willful infringement, the district court summarized the statements of which CellPro complains as follows:

The Court thus determined that both the '204 and '680 patents are valid and infringed by CellPro. Accordingly, there are no issues for you to decide concerning CellPro's liability for infringement of the '204 and '680 patents. In your deliberations you are bound to accept my determination that CellPro infringes these two patents, and that both patents are valid.

Joint App. at A26767. The jury instruction only separated considerations of liability and willfulness; we discern no error in that instruction.

CellPro next asserts that the court erred in failing to grant its renewed JMOL motion concerning willfulness. CellPro contends that a reasonable jury, upon consideration of its evidence, could not have found that its infringement was willful. Hopkins responds that the jury's finding of willfulness was supported by substantial evidence.

Willfulness is a question of fact to be proven by clear and convincing evidence. See SRI Int'l, Inc. v. Advanced Tech. Labs., Inc., 27 F.3d 1462, 1465, 44 USPQ2d 1422, 1424 (Fed. Cir. 1997) (noting that the "clear and convincing" evidentiary standard is appropriate because "'the boundary between unintentional

and culpable acts is not always bright,'" quoting Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1221, 36 USPQ2d 1225, 1232 (Fed. Cir. 1995)). Because CellPro had knowledge that it might infringe the Civin patents, it had an affirmative duty to exercise due care to avoid infringement. See SRI, 27 F.3d at 1464, 44 USPQ2d at 1423. CellPro attempted to discharge this duty by procuring legal opinions concerning the validity of the Civin patents and its infringement thereof. See Read Corp. v. Portec, Inc., 970 F.2d 816, 828, 23 USPQ2d 1426, 1437 (Fed. Cir. 1992) (noting that the duty to avoid infringement "normally entails obtaining advice of legal counsel although the absence of such advice does not mandate a finding of willfulness"). Our case law makes clear that legal opinions that conclude (even if ultimately incorrectly) that an infringer would not be liable for infringement may insulate an infringer from a charge of willful infringement if such opinions are competent (and followed). A opinion is competent if it is "thorough enough, as combined with other factors, to instill a belief in the infringer that a court might reasonably hold the patent is invalid, not infringed, or unenforceable." Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 944, 22 USPQ2d 1119, 1126 (Fed. Cir. 1992).

Substantial evidence supports the district court's conclusion that a reasonable jury could have concluded that the opinion letters were not adequate to defeat a finding of willfulness. Kiley, the CellPro representative who procured the opinion letters from Bloomberg, was highly sophisticated in matters of patent law and in the involved technology. Kiley had worked as a patent examiner and later was a partner at the law firm of Lyon & Lyon, where he handled patent prosecution and patent litigation. See Hopkins II, 978 F. Supp. at 187. It is therefore reasonable to conclude that Kiley should have been on notice concerning the opinions' obvious shortcomings and accordingly of the impropriety of CellPro's course of action. See, e.g., Underwater Devices, Inc. v. Morrison- Knudsen Co., 717 F.2d 1380, 1390, 219 USPQ 569, 576 (Fed. Cir. 1983). The opinions did not attempt to link the disclosures of the prior art references relied upon to establish anticipation or obviousness with the limitations of the claims of the patents. For example, and as the district court recognized, none of the allegedly anticipatory references cited in the '680 opinion letter even refers to a cell suspension. See Hopkins II, 978 F. Supp. at 194. The '204 opinion letter concluded that CellPro did not infringe claims 2, 3, 5, and 6 of the '204 patent, but conspicuously omitted any reference to claims 1 and 4, the claims asserted by Hopkins in this action. Further, the opinion letters are merely conclusory as to their allegations concerning inequitable conduct, and importantly make no mention that intent to deceive is a necessary component of this defense, a fact that is often difficult to establish. See Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 9 USPQ2d 1384 (Fed. Cir. 1988) (in banc). Such shortcomings should have been especially troublesome to a knowledgeable practitioner like Kiley, especially considering that the opinions did not express an opinion concerning infringement of the broadest claims. Further suspicion concerning CellPro's good faith exists in the record, but we find it unnecessary to summarize such evidence here. Under the circumstances, we cannot say that a reasonable jury could not have concluded that the opinion letters were ineffective to instill in CellPro, through Kiley, reasonable confidence that its activities did not infringe valid patents.

CellPro's final argument on willfulness is that the district court abused its discretion in deciding to treble Hopkins' damages under 35 U.S.C. § 284. Although Section 284 does not state a basis upon which a district court may increase damages, it is well established that enhancement of damages may be premised upon a finding of willful infringement. See, e.g., Beatrice Foods Co. v. New England Printing & Lithographing Co., 923 F.2d 1576, 1578, 17 USPQ2d 1553, 1555 (Fed. Cir. 1991). However, a finding of willful infringement does not mandate that the district court enhance damages; it merely authorizes the court to do so at its discretion. See Modine Mfg. Co. v. Allen Group, Inc., 917 F.2d 538, 543, 16 USPQ2d 1622, 1625 (Fed. Cir. 1990). In exercising this discretion, the trial court considers the weight of the evidence of the infringer's

culpability, see Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1581, 24 USPQ2d 1401, 1420 (Fed. Cir. 1992), in light of the factors included in Read. See note 16, supra (listing these factors).

CellPro's argument does not take issue with the district court's application of the Read factors. Instead, CellPro returns to its argument that the 1995 jury verdict reflects favorably on its lack of culpability because it illustrates the closeness of the case. See note 16, supra (fifth factor). We are once again not convinced that this temporary victory was significantly probative of CellPro's lack of culpability during the early stages of its infringing activity. We believe that the district court adequately justified its decision to treble the damages. See Hopkins II, 978 F. Supp. at 193-96; see also Read, 970 F.2d at 828, 23 USPQ2d at 1436 ("To enable appellate review, a district court is obligated to explain the basis for the [enhanced] reward, particularly when the maximum amount is imposed.").

To summarize, we find no error in either the jury's finding that CellPro willfully infringed the Civin patents or in the decision by the district court to treble damages; we accordingly affirm.

E. The Repatriation Order

CellPro's final argument is that the court exceeded the scope of its power when it ordered the repatriation and destruction of the six vials that it exported to its business partner, Biomira, in Canada, as well as cloned vials and antibodies produced therefrom. CellPro contends that it has not committed an infringing act with respect to the exported vials. CellPro summarizes its activities as follows: it produced approximately 100 vials of 12.8 hybridoma to create a United States master cell bank prior to the issuance of the '204 patent, it exported six of those vials to Canada after issuance, and it used those vials in Canada to supply markets outside of the United States. CellPro asserts that none of these acts—pre-issuance manufacture, export, or use outside of the United States—constitutes infringement under 35 U.S.C. § 271, and accordingly that such acts are beyond the scope of the court's equitable powers.

Hopkins responds that the district court's order was properly predicated on the determination that CellPro used (i.e., by cloning or testing) other vials from its United States cell bank in the United States after the issuance of the patent and thereby infringed with respect to the United States cell bank "as a whole." Hopkins asserts that the injunctive power of the district courts is not limited to the prohibition of those activities that constitute patent infringement, but also extends to prohibitions necessary in order to fashion a meaningful remedy for past infringement. Hopkins argues that repatriation in this case is such a meaningful remedy and will prevent CellPro from unfairly capitalizing upon its infringement.

Section 283 of the Patent Code empowers the courts to "grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283 (1994). In accordance with the clear wording of this section, "an injunction is only proper to the extent it is 'to prevent the violation of any right secured by patent.'" Eli Lilly & Co. v. Medtronic, Inc., 915 F.2d 670, 674, 16 USPQ2d 2020, 2024 (Fed. Cir. 1990) (quoting 35 U.S.C. § 283). A "necessary predicate" for the issuance of a permanent injunction is therefore a determination of infringement. Id. When deciding whether a district court abused the discretion provided by Section 283, we are mindful of the fact that the district courts are in the best position to fashion an injunction. See Joy Techs., Inc. v. Flakt, Inc., 6 F.3d 770, 777, 28 USPQ2d 1378, 1384 (Fed. Cir. 1993) (citation omitted). However, judicial restraint of lawful noninfringing activities must be avoided. See id. (citing Deepsouth Packing Co. v.

Laitram Corp., 406 U.S. 518, 529-31, 173 USPQ 769, 773-74 (1972)).

We agree with CellPro that the district court abused its discretion in ordering the repatriation and destruction of the exported vials. The repatriation aspect of the order does not enjoin activities that either have infringed the '204 patent or are likely to do so and thus does not prevent infringement—the proper purpose of an injunction under Section 283. It is clear that the six vials standing alone have not infringed the '204 patent. Mere possession of a product which becomes covered by a subsequently issued patent does not constitute an infringement of that patent until the product is used, sold, or offered for sale in the United States during the term of the patent. See Cohen v. United States, 487 F.2d 525, 527, 179 USPQ 859, 860 (Ct. Cl. 1973); Columbia & N.R.R. Co. v. Chandler, 241 F. 261 (9th Cir. 1917) (holding that, while the patentee could not recover damages for the manufacture of infringing trucks prior to the issuance of the patent, it did not follow "that the trucks were set free from the monopoly of the patent, and could thereafter be used, without liability to the inventor"); see also Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 304, 36 USPQ2d 1101, 1104 (Fed. Cir. 1995) ("[The patentee] may of course obtain damages only for acts of infringement after the issuance of the patent."). Likewise, neither export from the United States nor use in a foreign country of a product covered by a United States patent constitutes infringement. See 35 U.S.C. § 271(a) (1994) ("[W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent."); see also Paper Converting Mach. Co. v. Magna-Graphics Corp., 745 F.2d 11, 16, 223 USPQ 591, 594 (Fed. Cir. 1984) ("[B]y the terms of the patent grant, no activity other than the unauthorized making, using, or selling of the claimed invention can constitute direct infringement of a patent, no matter how great the adverse impact of that activity on the economic value of a patent.") (emphasis in original).

That CellPro used other vials from the cell bank in an infringing manner in the United States does not taint the six exported vials with infringement. The exported vials were not "guilty by association." One may consider the pre-issuance manufacture of two machines, one of which is used after the patent is issued and the other of which is exported. An injunction requiring return of the exported machine, which was never made, used, or sold during the term of the patent in the United States, is beyond the scope of Section 283 and hence an abuse of discretion. The same principle applies here to the vials exported to Canada. Accordingly, the court's conclusion that use of some of the vials of the cell bank constituted a use of the cell bank "as a whole" as a means of justifying its repatriation order was an abuse of discretion.

Moreover, there is also no evidentiary basis for concluding that the district court's order was necessary to prevent CellPro from committing further infringing activities. An injunction under Section 283 can reach extraterritorial activities such as those at issue here, even if these activities do not themselves constitute infringement. It is necessary however that the injunction prevent infringement of a United States patent. For example, in Spindelfabrik Suessen-Schurr v. Schubert & Salzer, 903 F.2d 1568, 14 USPQ2d 1913 (Fed. Cir. 1990), the infringer argued that the district court's injunction "impermissibly extend[ed] the reach of American patent law beyond the boundaries of the United States" because it prohibited the infringer from making, in Germany, machines "for use in the United States" and machines "destined for delivery to the United States." This court held that the injunction was "a reasonable and permissible endeavor to prevent infringement in the United States and not a prohibited extra-territorial application of American patent law. They were well within the district court's authority." Id. at 1578, 14 USPQ2d at 1921 (emphasis added).

The record in this case does not, as in Spindelfabrik, suggest that the exported vials will be used in a manner which will infringe the patent. CellPro has stipulated, and Hopkins does not refute, that Biomira intended to

produce antibodies for CellPro in Canada "for use in products to be sold outside of the United States." CellPro's Opening Brief at 40 (citing the declaration of John P. Bordonaro, at Joint App. A513, A515-16 ("At no time has CellPro imported back into the United States the 12.8 monoclonal antibodies manufactured by Biomira in Canada or the cell suspension derived from using the 12.8 monoclonal antibodies.")). Because the record is devoid of evidence upon which the district court could have concluded that its order would prevent further infringement, there was no basis for the court to order the exported hybridomas and its byproducts to be shipped to the United States.

We also do not find persuasive Hopkins' argument that the scope of the district court's order can be justified because it is necessary to fashion a meaningful remedy for CellPro's past infringement. Section 283 does not provide remedies for past infringement; it only provides for injunctive relief to prevent future infringement. The section under which a litigant must seek compensation for past infringement is Section 284. See 35 U.S.C. § 284, 1 (1994) ("Upon finding for the claimant the court shall award the claimant damages adequate to compensate for the infringement."). We do not understand Hopkins to seriously dispute that it has not received adequate compensation for CellPro's infringement. However, to the extent that Hopkins complains that CellPro's infringement has damaged its ability to service foreign markets, Hopkins must rely on foreign patent protection. See Deepsouth, 406 U.S. at 531, 173 USPQ at 774 ("Our patent system makes no claim to extraterritorial effect. . . . To the degree that the inventor needs protection in markets other than those of this country, the wording of 35 U.S.C. §§ 154 and 271 reveals a congressional intent to have him seek it abroad through patents secured in countries where his goods are being used.") (citations and quotation omitted). Such a complaint cannot be remedied by the imposition of an injunction under Section 283.

Hopkins further argues, mimicking the district court's "as a whole" rationale, that it would be fair under the circumstances to order repatriation and destruction because CellPro has committed other clear acts of infringement with respect to other vials in the United States cell bank. We do not agree. As we have already stated, we disagree that this rationale provides a sufficient premise for the court's order given the facts of this case. Moreover, premising the order on this rationale amounts to punishment of CellPro for its infringement. This is not the proper purpose of injunctive relief under Section 283. See Amstar Corp. v. Envirotech Corp., 823 F.2d 1538, 1549, 3 USPQ2d 1412, 1420 (Fed. Cir. 1987) (noting that "[p]unishment is not the purpose of an injunction" under Section 283 and citing Hecht Co. v. Bowles, 321 U.S. 321, 329 (1944), for the proposition that the "historic injunctive process was designed to deter, not to punish").

Those portions of the district court's permanent injunction order that ordered repatriation and destruction of vials exported by CellPro to Biomira and byproducts produced thereby are not consistent with the stated purpose of Section 283—to prevent infringement. Thus, the court abused its discretion, and those portions of the order are vacated.

Both sides have raised further arguments in support of their various positions. We have considered all such arguments, but they do not alter our conclusions.

CONCLUSION

The court erred in concluding that CellPro waived its right to rely on the Morstyn reference in establishing that the claims of the '680 patent are invalid under 35 U.S.C. § 103 (1994). We accordingly vacate the court's grant of summary judgment in favor of Hopkins and remand for further proceedings on this issue. The court also abused its discretion in ordering the repatriation and destruction of vials of hybridoma which CellPro

exported to Biomira in Canada and byproducts thereof. We accordingly vacate these portions of the court's permanent injunction order. The court did not err in any other respect. The decision of the court is therefore

AFFIRMED-IN-PART, VACATED-IN-PART and REMANDED.

Footnotes

1 The written description portions of both patents' specifications are identical.

2 The specification states that mature T-cells are a cause of GVHD in animals. See, e.g., '680 patent, col. 1, ll. 36-37.

3 "Monoclonal antibodies" are defined as "[a] population of identical antibodies . . . , all of which recognize the same specific [epitope] on a simple or complex antigen." Paul Singleton & Diana Sainsbury, Dictionary of Microbiology and Molecular Biology 431 (2d ed. 1993); see also Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369-70, 231 USPQ 81, 82 (Fed. Cir. 1986); In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

4 Fluorescence-activated coating separation ("FACS") "involves coating the antibody with a colored dye. All the cells in the coated sample then are passed through a machine that uses a laser to identify and separate the cells based on their color." Hopkins I, 931 F. Supp. at 309.

5 A "hybridoma" is defined as "[t]he product and/or progeny of cell fusion . . . between a [tumor] cell and a non-[tumor] cell; the in vitro production of hybridomas is carried out to provide continuously replicating (hybrid) cells which exhibit some or all of the characteristics of the non-[tumor] cell . . . ; such hybridomas are used, e.g., as sources of monoclonal antibodies." Singleton & Sainsbury, supra note 3, at 562.

6 Because the My-10 antigen disappears as a cell matures, but is present on all forms of stem cells, it is said to be "stage-specific," not lineage dependent. See '680 patent, col. 4, ll. 43-48.

7 Claim 1 of the '204 patent contains several other limitations which describe, for example, the specific cells on which the antigen is present. As the parties have not brought these limitations to our attention, we presume that the parties do not dispute that CellPro's antibody meets these limitations.

8 As stated by the trial court, "CellPro's process for purifying stem cells works as follows. CellPro adds blood cells to some of the 12.8 antibody that has been previously bound to biotin. These cells are poured into a column, inside of which are beads covered with avidin. Avidin binds tightly with biotin, locking the [stem] cells onto the walls of the column while the other [mature] cells are washed away. The column is then agitated to loosen the [stem] cells to obtain a purified suspension of stem cells." Hopkins I, 931 F. Supp. at 312.

9 Apparently because neither CellPro's Ceprate machines nor its production of 12.8 antibody directly infringed the "cell suspension" claims of the '680 patent, Hopkins sued CellPro for inducing infringement and contributory infringement. See Hopkins I, 931 F. Supp. at 307.

10 Table 9 indicates that "3% of the FACS-Separated My-10-antigen-positive cells were matured neutrophils . . . , 6% were mature monocytes, and 1% were mature lymphocytes." '680 patent, col. 18, tbl. 9 n.*. Thus, there are 3% + 1% + 6% = 10% mature cells in the disclosed cell suspension.

"Neutrophils," "monocytes," and "lymphocytes" are defined as types of "leucocytes," which in turn are defined as "the white cells of the blood and lymphoid system." Singleton & Sainsbury, supra note 3, at 498.

11 Specifically, CellPro proffered two expert declarations, one from Dr. H. Mark Jones concluding that Morstyn anticipated the claims, and one from Dr. C. Glenn Begley concluding that the claims were either "anticipated and/or obvious in view of [Beverly] and/or [Morstyn]."

12 Although the court expressly rejected only Jones's testimony, we interpret the court's reasoning to have precluded any argument that relied on Morstyn, including the argument that Beverly in combination with Morstyn would have rendered the asserted claims obvious.

On May 6, 1998, CellPro informed this court that, in response to the district court's invitation, CellPro subsequently briefed the district court on the issue of admissibility of Jones's testimony. After Hopkins had the opportunity to respond, the district court declined to reconsider its prior decision on this issue. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jan. 17, 1997) (transcript).

13 "CD" stands for "cluster designation," which is used by those skilled in the art to group together antibodies that exhibit similar binding characteristics, particularly binding to the same antigen. As explained by CellPro in its brief to this court: "[i]n an attempt to classify and to organize the large numbers of new blood cell antibodies that are generated in laboratories each year, panels of scientists review research data and designate clusters of antibodies that appear to have similar binding characteristics. CD34 is the 34th cluster so designated." CellPro's Opening Brief at 5 n.2. Thus, although "CD34" technically refers to a genus of antibodies that bind to a particular entity, scientists generally refer to that entity as "the CD34 antigen." Both parties generally agree that the anti-My- 10 and 12.8 antibodies have been properly classified as CD34 antibodies.

14 The Kohler/Milstein method involves first immunizing a mouse with a human cell [the immunogen], which makes the mouse capable of producing the relevant antibody. The mouse's B cells, the ones that produce antibodies, are then removed and chemically fused with an immortal cancer cell line from a mouse. The fused cells, called hybridomas, will have the combined qualities of a B cell and the cancer cell line—they will be immortal and they will have the ability to make one antibody. The hybridomas are then screened to discover an antibody that has the characteristic being sought, in this case one that binds to an antigen on stem cells but not on mature cells.

Hopkins I, 931 F. Supp. at 309. Civin used a human immortal cancer cell line, known as KG-1a, as the immunogen in this process. Civin knew that these cells had characteristics similar to immature cells and therefore that they might have similar antigens on their surfaces and might stimulate the production of antibodies capable of binding to antigens on immature stem cells. See id.

15 35 U.S.C. § 284, 2 (1994) provides in relevant part that "the court may increase the damages up to three times the amount found or assessed" in a patent infringement action.

16 These factors include: (1) whether the infringer deliberately copied the ideas or design of another, (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed, (3) the infringer's behavior as a party to the litigation, (4) the infringer's size and financial condition, (5) the closeness of the case, (6) the duration of the infringer's misconduct, (7) any remedial action by the infringer, (8) the infringer's motivation for harm, and

(9) whether the infringer attempted to conceal its misconduct. See Read, 970 F.2d at 827, 23 USPQ2d at 1435-36.

17 CellPro also notes that the applicant referred to this purported definition of the words "substantially free" during the reexamination of the '680 patent, at which time the applicant was attempting to distinguish its claims over the Beverley reference. Because the relevant excerpts from the reexamination prosecution history are largely redundant with the prosecution history summarized above, we do not reiterate them here.

18 Hopkins intimates in its brief that the specification discloses other cell suspensions of lesser purities, but it has not specifically identified them and we do not find them in the specification.

19 Equally unremarkable is the confirmation of the patentability of the claims during reexamination over the Beverley reference, which the applicant and the examiner agreed were "significantly contaminated with small lymphocytes," including T-cells.

20 "After [a pretrial] conference held pursuant to this rule, an order shall be entered reciting the action taken. This order shall control the subsequent course of the action unless modified by a subsequent order. The order following a final pretrial conference shall be modified only to prevent manifest injustice." Fed. R. Civ. P. 16(e).

21 We note that although the court granted a new trial on the issue of obviousness, it was not improper for CellPro to subsequently present an argument that the claims were anticipated: "[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983) (citing In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982)).

22 We express no opinion as to whether summary judgment may or may not be appropriate upon remand.

23 Hopkins also points out that the examiner subsequently placed her imprimatur on the idea that My-10 and "the CD34 antigen" were synonymous, noting that the claims were limited to those monoclonal antibodies reactive with "a particular antigen (now identified as CD34)." See Joint App. at EA7954.

24 An "epitope" is defined as "any region of the [antigen] macromolecule with the ability or potential to elicit, and combine with, specific antibody." Singleton & Sainsbury, supra note 3, at 269, 323.

25 The Kg-1a cell line is a variant of the Kg-1 cell line. See '204 patent, col. 3, ll. 44-47. Both of these cell lines and samples of the hybridoma produced thereby are readily available to the public, and the '204 patent discloses the locations at which both of these starting materials may be procured. Such public deposits of living materials may enable a claimed invention whose manufacture or use depends thereupon, see, e.g., Wands, 858 F.2d at 735 & n.8, 8 USPQ2d at 1403 & n.8, but Hopkins does not attempt to refute CellPro's enablement challenge by relying on these deposits. In any event, because we conclude that CellPro's challenge fails even without consideration of the deposits, we need not comment on their relevance.

26 The district court noted that "[t]estimony at trial established that a person skilled in the art of making monoclonal antibodies must have a bachelor's degree in the appropriate scientific field and must have made a monoclonal antibody at least once." Hopkins I, 931 F. Supp. at 323. CellPro does not contest this definition of one of ordinary skill in this art.

27 Dr. C.E. Van der Schoot's expert declaration filed in opposition to Hopkins' summary judgment motion is inapposite for the same reason. Van der Schoot concluded "that there were numerous differences between [the] immunization protocol [which we] used to obtain three monoclonal CD34 antibodies . . . and Dr. Civin's immunization protocol disclosed in the '204 patent." Joint App. at A23420. The deposition testimony of Dr. Gustav Gaudernack, also relied on by CellPro, evidences a similar failing to follow the disclosure of the '204 patent. Gaudernack testified that he followed neither the disclosed immunization protocol nor the disclosed screening protocol. See id. at A22612.

28 Wijdenes opined that the KG-1 and KG-1a cell lines are equivalent immunogens for purposes of producing CD34 antibodies. See Joint App. at A23343.

29 Finally, we note that Wijdenes, like Van der Schoot and Gaudernack, see note 27, supra, "did not copy the protocol described in [the '204 patent] specification," Joint App. at A23361. This provides yet another reason for concluding that Wijdenes's testimony did not bear significantly on enablement.

30 In Datascope, the district court helped to justify its conclusion that the infringer did not act willfully by noting that this court had earlier split 2-1 in affirming the judgment that the infringer was liable. The district court felt that this court's non-unanimity buttressed "an honest doubt . . . as to the validity and infringement of Datascope's patents" as reflected in legal opinions which the infringer procured during the development of its infringing device. Datascope, 879 F.2d at 823, 11 USPQ2d at 1323. We reversed the finding of nonwillfulness, stating:

The district court's reference to this court's 2-1 decision affirming the judgment of liability was inappropriate in this case. That decision was rendered several years after the date infringement began (i.e., the date employed in determining willfulness under the circumstances of this case), and was based on facts unrelated to [the infringer's] decision on the critical date.

Id. at 828, 11 USPQ2d at 1327 (citations omitted).

31 We do not suggest, and neither party argues, that the court had no injunctive power with respect to those vials which were not exported but which were also not used in the United States. That these vials, like the exported vials, did not infringe does not free them from the court's equitable power under Section 283. Because CellPro had used some of its vials in the United States, a clear act of infringement, its propensity to infringe has been sufficiently established such that the court could conclude that enjoining the use of United States-based vials was necessary to prevent infringement.

The specification states that mature T-cells are a cause of GVHD in animals. See, e.g., '680 patent, col. 1, ll. 36-37. "Monoclonal antibodies" are defined as "[a] population of identical antibodies . . . , all of which recognize the same specific [epitope] on a simple or complex antigen." Paul Singleton & Diana Sainsbury, Dictionary of Microbiology and Molecular Biology 431 (2d ed. 1993); see also Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369-70, 231 USPQ 81, 82 (Fed. Cir. 1986); In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Fluorescence-activated coating separation ("FACS") "involves coating the antibody with a colored dye. All the cells in the coated sample then are passed through a machine that uses a laser to identify and separate the cells based on their color." Hopkins I, 931 F. Supp. at 309. A "hybridoma" is defined as "[t]he product and/or progeny of cell fusion . . . between a [tumor] cell and a non-[tumor] cell; the in vitro production of hybridomas is carried out to provide continuously replicating (hybrid) cells which exhibit some or all of the characteristics of the non-[tumor] cell . . . ; such hybridomas are

used, e.g., as sources of monoclonal antibodies." Singleton & Sainsbury, supra note 3, at 562. Because the My-10 antigen disappears as a cell matures, but is present on all forms of stem cells, it is said to be "stage-specific," not lineage dependent. See '680 patent, col. 4, ll. 43-48. Claim 1 of the '204 patent contains several other limitations which describe, for example, the specific cells on which the antigen is present. As the parties have not brought these limitations to our attention, we presume that the parties do not dispute that CellPro's antibody meets these limitations. As stated by the trial court, "CellPro's process for purifying stem cells works as follows. CellPro adds blood cells to some of the 12.8 antibody that has been previously bound to biotin. These cells are poured into a column, inside of which are beads covered with avidin. Avidin binds tightly with biotin, locking the [stem] cells onto the walls of the column while the other [mature] cells are washed away. The column is then agitated to loosen the [stem] cells to obtain a purified suspension of stem cells." Hopkins I, 931 F. Supp. at 312. Apparently because neither CellPro's Ceprate machines nor its production of 12.8 antibody directly infringed the "cell suspension" claims of the '680 patent, Hopkins sued CellPro for inducing infringement and contributory infringement. See Hopkins I, 931 F. Supp. at 307. Table 9 indicates that "3% of the FACS-Separated My-10-antigen-positive cells were matured neutrophils . . . , 6% were mature monocytes, and 1% were mature lymphocytes." '680 patent, col. 18, tbl. 9 n.*. Thus, there are 3% + 1% + 6% = 10% mature cells in the disclosed cell suspension. "Neutrophils," "monocytes," and "lymphocytes" are defined as types of "leucocytes," which in turn are defined as "the white cells of the blood and lymphoid system." Singleton & Sainsbury, supra note 3, at 498. Specifically, CellPro proffered two expert declarations, one from Dr. H. Mark Jones concluding that Morstyn anticipated the claims, and one from Dr. C. Glenn Begley concluding that the claims were either "anticipated and/or obvious in view of [Beverly] and/or [Morstyn]." Although the court expressly rejected only Jones's testimony, we interpret the court's reasoning to have precluded any argument that relied on Morstyn, including the argument that Beverly in combination with Morstyn would have rendered the asserted claims obvious. On May 6, 1998, CellPro informed this court that, in response to the district court's invitation, CellPro subsequently briefed the district court on the issue of admissibility of Jones's testimony. After Hopkins had the opportunity to respond, the district court declined to reconsider its prior decision on this issue. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jan. 17, 1997) (transcript). "CD" stands for "cluster designation," which is used by those skilled in the art to group together antibodies that exhibit similar binding characteristics, particularly binding to the same antigen. As explained by CellPro in its brief to this court: "[i]n an attempt to classify and to organize the large numbers of new blood cell antibodies that are generated in laboratories each year, panels of scientists review research data and designate clusters of antibodies that appear to have similar binding characteristics. CD34 is the 34th cluster so designated." CellPro's Opening Brief at 5 n.2. Thus, although "CD34" technically refers to a genus of antibodies that bind to a particular entity, scientists generally refer to that entity as "the CD34 antigen." Both parties generally agree that the anti-My- 10 and 12.8 antibodies have been properly classified as CD34 antibodies. The Kohler/Milstein method involves first immunizing a mouse with a human cell [the immunogen], which makes the mouse capable of producing the relevant antibody. The mouse's B cells, the ones that produce antibodies, are then removed and chemically fused with an immortal cancer cell line from a mouse. The fused cells, called hybridomas, will have the combined qualities of a B cell and the cancer cell line—they will be immortal and they will have the ability to make one antibody. The hybridomas are then screened to discover an antibody that has the characteristic being sought, in this case one that binds to an antigen on stem cells but not on mature cells. Hopkins I, 931 F. Supp. at 309. Civin used a human immortal cancer cell line, known as KG-1a, as the immunogen in this process. Civin knew that these cells had characteristics similar to immature cells and therefore that they might have similar antigens on their surfaces and might stimulate the production of antibodies capable of binding to antigens on immature stem cells. See id. 35 U.S.C. § 284, 2 (1994) provides in relevant part that "the court

may increase the damages up to three times the amount found or assessed" in a patent infringement action. These factors include: (1) whether the infringer deliberately copied the ideas or design of another, (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed, (3) the infringer's behavior as a party to the litigation, (4) the infringer's size and financial condition, (5) the closeness of the case, (6) the duration of the infringer's misconduct, (7) any remedial action by the infringer, (8) the infringer's motivation for harm, and (9) whether the infringer attempted to conceal its misconduct. See Read, 970 F.2d at 827, 23 USPQ2d at 1435-36. CellPro also notes that the applicant referred to this purported definition of the words "substantially free" during the reexamination of the '680 patent, at which time the applicant was attempting to distinguish its claims over the Beverley reference. Because the relevant excerpts from the reexamination prosecution history are largely redundant with the prosecution history summarized above, we do not reiterate them here. Hopkins intimates in its brief that the specification discloses other cell suspensions of lesser purities, but it has not specifically identified them and we do not find them in the specification. Equally unremarkable is the confirmation of the patentability of the claims during reexamination over the Beverley reference, which the applicant and the examiner agreed were "significantly contaminated with small lymphocytes," including T-cells. "After [a pretrial] conference held pursuant to this rule, an order shall be entered reciting the action taken. This order shall control the subsequent course of the action unless modified by a subsequent order. The order following a final pretrial conference shall be modified only to prevent manifest injustice." Fed. R. Civ. P. 16(e). We note that although the court granted a new trial on the issue of obviousness, it was not improper for CellPro to subsequently present an argument that the claims were anticipated: "[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983) (citing In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982)). We express no opinion as to whether summary judgment may or may not be appropriate upon remand. Hopkins also points out that the examiner subsequently placed her imprimatur on the idea that My-10 and "the CD34 antigen" were synonymous, noting that the claims were limited to those monoclonal antibodies reactive with "a particular antigen (now identified as CD34)." See Joint App. at EA7954. An "epitope" is defined as "any region of the [antigen] macromolecule with the ability or potential to elicit, and combine with, specific antibody." Singleton & Sainsbury, supra note 3, at 269, 323. The Kg-1a cell line is a variant of the Kg-1 cell line. See '204 patent, col. 3, ll. 44-47. Both of these cell lines and samples of the hybridoma produced thereby are readily available to the public, and the '204 patent discloses the locations at which both of these starting materials may be procured. Such public deposits of living materials may enable a claimed invention whose manufacture or use depends thereupon, see, e.g., Wands, 858 F.2d at 735 & n.8, 8 USPQ2d at 1403 & n.8, but Hopkins does not attempt to refute CellPro's enablement challenge by relying on these deposits. In any event, because we conclude that CellPro's challenge fails even without consideration of the deposits, we need not comment on their relevance. The district court noted that "[t]estimony at trial established that a person skilled in the art of making monoclonal antibodies must have a bachelor's degree in the appropriate scientific field and must have made a monoclonal antibody at least once." Hopkins I, 931 F. Supp. at 323. CellPro does not contest this definition of one of ordinary skill in this art. Dr. C.E. Van der Schoot's expert declaration filed in opposition to Hopkins' summary judgment motion is inapposite for the same reason. Van der Schoot concluded "that there were numerous differences between [the] immunization protocol [which we] used to obtain three monoclonal CD34 antibodies . . . and Dr. Civin's immunization protocol disclosed in the '204 patent." Joint App. at A23420. The deposition testimony of Dr. Gustav Gaudernack, also relied on by CellPro, evidences a similar failing to follow the disclosure of the '204 patent. Gaudernack testified that he followed neither the disclosed immunization protocol nor the disclosed screening protocol. See id. at

A22612. Wijdenes opined that the KG-1 and KG-1a cell lines are equivalent immunogens for purposes of producing CD34 antibodies. See Joint App. at A23343. Finally, we note that Wijdenes, like Van der Schoot and Gaudernack, see note 27, supra, "did not copy the protocol described in [the '204 patent] specification," Joint App. at A23361. This provides yet another reason for concluding that Wijdenes's testimony did not bear significantly on enablement. In Datascope, the district court helped to justify its conclusion that the infringer did not act willfully by noting that this court had earlier split 2-1 in affirming the judgment that the infringer was liable. The district court felt that this court's non-unanimity buttressed "an honest doubt . . . as to the validity and infringement of Datascope's patents" as reflected in legal opinions which the infringer procured during the development of its infringing device. Datascope, 879 F.2d at 823, 11 USPQ2d at 1323. We reversed the finding of nonwillfulness, stating: The district court's reference to this court's 2-1 decision affirming the judgment of liability was inappropriate in this case. That decision was rendered several years after the date infringement began (i.e., the date employed in determining willfulness under the circumstances of this case), and was based on facts unrelated to [the infringer's] decision on the critical date. Id. at 828, 11 USPQ2d at 1327 (citations omitted). We do not suggest, and neither party argues, that the court had no injunctive power with respect to those vials which were not exported but which were also not used in the United States. That these vials, like the exported vials, did not infringe does not free them from the court's equitable power under Section 283. Because CellPro had used some of its vials in the United States, a clear act of infringement, its propensity to infringe has been sufficiently established such that the court could conclude that enjoining the use of United States-based vials was necessary to prevent infringement.